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Tamiflu reduces risk of death by 25 percent in adults hospitalised with H1N1 pandemic influenza

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Adults hospitalised with H1N1 influenza during the 2009-2010 pandemic were 25% less likely to die from the disease if they were given antiviral drugs called neuraminidase inhibitors (NAIs) such as Tamiflu, according to a large meta-analysis involving more than 29 000 patients from 38 countries, published in *The Lancet Respiratory Medicine* journal. The findings also indicate that treatment within 2 days of flu symptoms developing halved the risk of death compared with later treatment or no treatment.

"Many governments have stockpiles of Tamiflu that are close to expiry. But until now, they had no adequate data to assist them in deciding if lives were saved in 2009-2010 or not, and whether they should replenish or not", explains lead author Professor Jonathan Nguyen-Van-Tam, from the University of Nottingham in the UK.

"The situation is made more complex by the fact that when an influenza pandemic occurs, even with the best will in the world, vaccine arrives six months too late and its public health benefit is therefore moderate at best. Thus we are left with antivirals like Tamiflu and public health measures like handwashing and social distancing as the only defences we have for the first 6 months of a pandemic."

Nguyen-Van-Tam, and colleagues from the Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE) research consortium, did a

meta-analysis of individual patient data to assess the effects of NAI treatment (primarily Tamiflu) on death in patients hospitalised with confirmed or suspected H1N1 infection between January 2, 2009 and March 14, 2011. Using statistical modelling, the researchers compensated for the effects of treatment propensity (likelihood of treatment) as well as other confounding factors such as treatment with corticosteroids and antibiotics and health-care seeking behaviour.

Analysis of data from 78 studies involving 29 234 patients of all ages revealed that treatment with NAIs (at any time) reduced the risk of death by 19%, compared with no treatment.

The researchers report that to maximise survival, ideally NAIs should be started within 2 days of symptoms developing. The risk of death was halved when starting treatment within 48 hours of symptom onset compared with later treatment, or no antiviral treatment. Each day that starting antiviral treatment was delayed after 2 days from illness onset was associated with about a 20% increase in the risk of death compared with treatment started within 2 days.

Importantly, they noted much the same survival benefit in pregnant women and adult patients in intensive care with more severe symptoms, but observed no significant mortality reduction in children.

According to Professor Nguyen-Van-Tam, "Since placebo-controlled trials of NAIs are not ethically feasible during a pandemic, the evidence we have assembled is likely to be the best that is available. Our data suggest that in line with US Centers for Disease Control and Prevention recommendations, treatment guidance policies should emphasise that NAI treatment should be started as soon as possible for any hospitalised adult who presents with influenza that is suspected or confirmed. Since so many patients with severe influenza are not admitted to hospital within 48 hours of symptom onset, the same applies to adults in the

community who are appreciably unwell with influenza like illness or who have underlying risk conditions. If clinical suspicion is high, one should not wait for laboratory confirmation before starting treatment."

Writing in a linked Comment, Alicia Fry from the Centers for Disease Control and Prevention in the USA says, "As expected, early treatment seems to be optimal, and treatment shouldn't be delayed by even 1 day to wait for diagnostic test results; however, if the patient presents for care more than 2 days after illness onset, treatment might still have some benefit, especially if they are severely ill. Although additional evidence for the benefits of NAI treatment in children admitted to hospital, and how to optimise treatment, are needed, in the absence of any other influenza-specific treatment, the potential benefit from NAI treatment for severely ill children is substantial and outweighs any potential risk associated with treatment."

She concludes, "Continuing efforts to identify other anti-influenza treatment options, especially those with different virus targets or mechanisms of action, might improve our ability to care for severely ill patients with influenza and reduce the risk of mortality further."

Provided by Lancet